THE CHILDREN'S CAUSE INC.

Mobilizing to conquer
childhood cancer

July 5, 2002

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane – Room 1061
Rockville, MD 20652

Docket Number 02N-0152

Dear Sir or Madam:

The Children's Cause, a national patient education and advocacy group, is dedicated to accelerating the pace of innovative, safer, more effective therapies for childhood cancer. Despite advances in recent years, childhood cancer remains the leading disease killer of children.

We are pleased to have the opportunity to comment on the relationship between the 1998 Pediatric Rule and the recently enacted Best Pharmaceuticals for Children Act (BPCA). These two strategies for increasing information about the uses of drugs in children have proved directly beneficial to thousands of children with a variety of disorders. For children with cancer, however, the application of the Pediatric Rule and the BPCA require substantial clarification.

Background

Pediatric cancer research differs from that of other childhood diseases in that it is driven by a nationwide, government-funded academic network of pediatric oncologists, who enroll most pediatric cancer patients in clinical trials. Cytotoxic drugs approved for use in adult cancers typically have been tested in children eventually in combination therapy through NCI-sponsored cooperative groups and cancer centers. Effective treatments in pediatric oncology have evolved from researchers' familiarity with safety and efficacy data from the scientific literature. Marketed anti-cancer agents used in children are not labeled for pediatric use.

The cooperative group research strategy has resulted in dramatic increases in survival rates over the past 25 years for certain types of childhood cancer. This history of successful treatment of childhood cancer calls into question FDA's strict interpretation of labeling requirements for pediatric uses of oncology drugs in the application of both the Pediatric Rule and the incentive in BPCA.

Childhood cancer consists of many different diseases, each of which affects just a few hundred children a year. While there are 12,400 children diagnosed per year, there are at least 12 different histological types of cancer and many more divisions to come, as investigators find that particular tumors, once thought to be unified constructs, are actually comprised of genetically distinct subtypes, which can have very different treatment outcomes. Small sample sizes on which to evaluate the safety and efficacy of a single agent mean that it can take at least 10 years for a new anti-cancer agent to be incorporated into Phase III pediatric trials.

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Few children on which to evaluate any new anti-cancer therapy also means that a decision to conduct pediatric studies of any one agent commits children with that type of cancer for many years to come. Introducing an agent into clinical trials for children with cancer also precludes the evaluation of other perhaps more promising alternatives.

Advances in molecularly targeted approaches to cancer therapy are now resulting in a pipeline of many new, potentially more effect anti-cancer agents likely to have fewer short term and long term toxicities. These drugs offer hope of more effective treatments for life threatening childhood cancers, including hard to treat solid tumors, like brain tumors, where survival rates remain poor.

Families expect FDA to implement both the Pediatric Rule and the BPCA in a manner that will enable pediatric testing of anti-cancer agents to be based on the best available scientific evidence. FDA needs to publicly acknowledge how the rule and the incentive will be applied to assure that children currently diagnosed with cancer will have the greatest likelihood of therapeutic benefit in clinical trials, and the treatment of children yet to be diagnosed can build on past clinical research.

Recommendations

- **As intended by the BPCA, the Pediatric Subcommittee of Oncologic Drugs Advisory Committee (ODAC) should clarify its mission and membership, be reconvened as soon as possible, and meet on a regular, published schedule.**

The BPCA specifies that the Pediatric Subcommittee of ODAC should have representatives of all major constituents in the pediatric oncology community. Further, it should serve as the forum to develop and recommend strategies for prioritizing agents for study so as to increase the likelihood that the most promising agents for children are brought into clinical trials and that patient resources are conserved.

- **FDA should formally acknowledge that the notion of "same disease" or "same indication" in cancer in children and adults is subject to evolving scientific understanding. Such clarification should indicate that each disease type must be decided on a case by case basis based on advice from the Pediatric Subcommittee of ODAC, other extramural experts and the latest scientific evidence.**

FDA's stated requirement of disease equivalence or of "same indication" when applying the rule and the incentive does not fit current scientific understanding of most childhood cancers. This issue was the subject of several earlier meetings of the Pediatric Subcommittee of ODAC, where discussion among researchers differed widely about how and under what circumstances childhood cancers could be considered the same as adult cancers. Published guidelines from FDA about its approach to this issue in the review of oncology agents could strengthen cooperative group researchers' efforts to obtain drugs from companies for pediatric testing and clarify companies' understanding of the likelihood that the rule or the incentive might apply to the agent under development.

- **FDA should award six months of exclusivity for oncology drugs when the adult safety and efficacy data make it a promising candidate for treating childhood cancer, if a company enables pediatric testing while the agent is in adult Phase II adult testing.**

Companies are reluctant to allow early testing of an agent in development out of concern that negative or adverse results in a pediatric study may jeopardize FDA approval for an adult

indication regardless of FDA's statements that this has never occurred. Awarding six months of exclusivity for pediatric studies of an agent prior to its approval for adults may encourage companies to take risks, although pediatric testing would still be voluntary.

- **FDA should consider the application of the Pediatric Rule to oncology drugs and biologics in development when there is broad, open, and current agreement among pediatric oncology researchers, through the Pediatric ODAC and other extramural expert opinion, that the cancers to be studied in children are clearly understood as "the same" as those occurring in adults.**

If preclinical and/or safety and efficacy data indicate that agents have valid and therapeutically important parallels between adult and pediatric cancer, and if companies are unwilling to test promising pre-approved oncology agent early in pediatric trials, application of the rule is likely to enable pediatric access to such agents.

- **Without compromising standards for high quality trials, FDA should not apply strict labeling requirements for agents to treat children with cancer when implementing the Pediatric Rule or the incentive.**

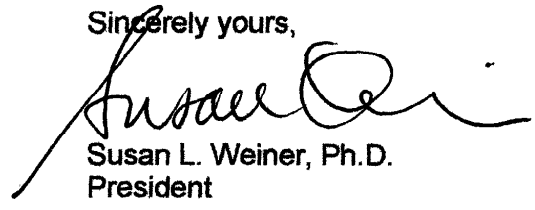
Past and future progress in childhood cancer depends on cooperative group and cancer center trials designed by pediatric oncology researchers, which, when published in peer reviewed literature, establish standards of care. Requiring pediatric labeling now for marketed or for new agents can only disrupt established patterns of pediatric cancer research and delay children's access to new therapies.

- **FDA should create a single center for oncology review to ensure that consistent standards in evaluating anti-cancer drugs and biologics for children are applied.**

Because the Pediatric Rule can apply to biologics but the incentive cannot under current law, a single center for oncology review is likely to help unify FDA's approach and standards to testing agents in pediatric cancer. It could also to help conserve patient resources as FDA's deliberations about oncology agents in pediatric clinical trials would be brought into a central unit.

As families and survivors whose loved ones have struggled with childhood cancer, we appreciate the chance to offer recommendations to FDA on the implementation of the Pediatric Rule and the BPCA, and urge FDA to hasten the application of safe and effective therapies for our children.

Sincerely yours,



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446